1: Microvasc Res. 2002 Jul;64(1):135-47. Related Articles, Links

Mechanisms which mediate the antiapoptotic effects of angiopoietin-1 on endothelial cells.

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The main objective of this study was to identify molecular mechanisms through which angiopoietin-1 (Ang-1), a ligand for Tie-2 receptors, influences endothelial cell apoptosis. Human umbilical vein endothelial cells were cultured in a medium enriched with 2% fetal bovine serum (FBS) and growth supplements. Apoptosis was induced over 24 h by reducing FBS to 0.1%. Activation of caspase-9, -8, -7, and -3 and the expression of Bcl-2 family proteins, inhibitors of apoptosis (IAPs), cytochrome c, as well as Smac proteins were evaluated with immunoblotting. Ang-1 clearly attenuated serum deprivation-evoked apoptosis, an effect which required Tie-2 receptor activation. Activation of caspase-9, -7, and -3, but not caspase-8, was inhibited by Ang-1. The inhibitory effects of Ang-1 on apoptosis and caspase activation were reversed by a PI-3 kinase inhibitor (wortmannin). Ang-1 exposure upregulated the expression of Survivin but not XIAP (members of IAPs), reduced the cystosolic levels of Smac, but not that of cytochrome c, and had no effect on the expression of Bcl-2 family proteins. This is the first study to report on the mitochondrial mechanisms through which Ang-1 inhibits apoptosis and to investigate the role of the newly discovered Smac. We conclude that Ang-1 inhibits endothelial cell apoptosis through several pathways, which include PI-3 kinase/AKT activation, inhibition of Smac release from the mitochondria, and upregulation of Survivin protein.

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1: Eur J Pharmacol. 1996 Dec 27;318(1):93-6.

Potent inhibition of angiogenesis by wortmannin, a fungal metabolite.

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Wortmannin ([1S-(1 alpha, 6b alpha, 9a beta, 11 alpha, 11b beta)]-11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a, 11b-dimethyl-3 H-furo[4,3,2-de]indeno [4,5-h]-2-benzopyran-3,6,9-trione), a fungal metabolite that is as a selective inhibitor of phosphatidylinositol 3-kinase, was evaluated for its potential as an inhibitor of in vivo angiogenesis in a bioassay system involving growing chick embryo chorioallantoic membranes. It showed dose-dependent inhibitory activity against embryonic angiogenesis. This inhibition occurred at a dose as low as 1 ng (2.3 pmol) per egg and the ID50 value was 30 ng/egg. These findings suggest that wortmannin is a new angiogenesis inhibitor, and that it may be a lead antibiotic for a novel class of therapeutic agents for angiogenesis-dependent diseases like cancer, diabetic retinopathy and rheumatoid arthritis.

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